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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO
09/842,469	04/26/2001	Leonard Buckbinder	pc10873B	7996

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EXAMINER
MOORE, WILLIAM W

ART UNIT	PAPER NUMBER
1652	13

DATE MAILED: 09/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Application No.	Applicant(s)
09/842,469	BUCKBINDER ET AL.
Examiner	**Art Unit**
William W. Moore	1652

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)[·] Responsive to communication(s) filed on *16 June 2003*.

2a)[·] This action is **FINAL**. 2b)[ ] This action is non-final.

3)[ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)[·] Claim(s) *14 and 19-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)[ ] Claim(s) _____ is/are allowed.

6)[·] Claim(s) *14 and 19-39* is/are rejected.

7)[ ] Claim(s) _____ is/are objected to.

8)[ ] Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)[·] The specification is objected to by the Examiner.

10)[ ] The drawing(s) filed on _____ is/are: a)[ ] accepted or b)[ ] objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)[ ] The proposed drawing correction filed on _____ is: a)[ ] approved b)[ ] disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)[ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)[ ] Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)[ ] All b)[ ] Some * c)[ ] None of:

1.[ ] Certified copies of the priority documents have been received.

2.[ ] Certified copies of the priority documents have been received in Application No. _____.

3.[ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)[ ] Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

Attachment(s)

1) [ ] Notice of References Cited (PTO-892)
2) [ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) [ ] Information Disclosure Statement(s) (PTO-1449) Paper No(s).
4) [ ] Interview Summary (PTO-413) Paper No(s).
5) [ ] Notice of Informal Patent Application (PTO-152)
6) [ ] Other

DETAILED ACTION

Response to Amendment

Applicant's Amendment B filed June 16, 2003, was entered, canceling claims 1-13 and 15-18, adding new claims 19-39, and amending claim 14 to depend from claim 19. The new claims describe genera of variant metalloproteases included within the genera described at page 3, lines 22-26, of the specification, thus present no new matter. Claim 19 requires that a polypeptide of the invention be "purified", as do each of claims 14 and 20-39 that depend from it, avoiding the rejection of originally-filed claims 5 and 6 under 35 U.S.C. §101 in the communication mailed February 13, 2003, for description of non-statutory subject matter. The new claims avoid the prior art rejection of record herein over the U.S. Patent No. 6,391,610 to Apte et al. because claim 19, from which all pending claims depend, requires all members of the many polypeptide genera embraced by the dependent claims to comprise at least an amino acid sequence region that is "90% identical" to the 387-amino acid metalloprotease domain present, see legend of Figure 3, between positions 67 through 543, inclusive, of SEQ ID NO:2. The corresponding region in the ADAMTS-10 metalloprotease of Apte et al. shares only 89% identity with the critical domain of claim 19. Such is not the case with the prior art rejection of record over Heller et al., which is maintained as to claims 14, 19-23 and 30-34 because both the prior art prodomain and metalloprotease domain meet limitations of claims 19-23 and 30-34. Heller et al. is not prior art to the new claims 24-29 and 35-39, however, because the disintegrin domain and the single thrombospondin domain in the metalloprotease of Heller et al. differ substantially from the disintegrin domain at positions 469-531 of SEQ ID NO:2 herein, and the thrombospondin domains at positions 548 to 601, positions

30-34 to incorporate limitations of claims 24-29 and 35-39 will not remove the domains

claims from the rejections of record under 35 U.S.C. §§101 and 112, first paragraph, which are maintained as explained below.

Specification

The disclosure is objected to because of the following informalities: The disclosure is objected to because it contains an embedded hyperlink, page 1 at line 13, and/or other form of browser-executable code. Applicant is required to delete this occurrence of, and any other occurrence of, an embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. §101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 14 and 19-39 are rejected, essentially for reasons of record, under 35 U.S.C. §101 because the claimed invention lacks patentable utility.

Applicant's arguments filed June 16, 2003, have been fully considered but they are not persuasive. Applicant suggests at pages 7-9 of the Paper filed June 16, 2003, that the ADAMTS-E metalloprotease having the amino acid sequence set forth in SEQ ID NO:2 herein might be considered to have a specific and substantial activity as an aggrecanase because it "is a member of the family of proteins known as ADAMTS proteins", which "exhibit(s) characteristics of the well-characterized ADAM family of metalloproteases". Applicant alleges that members of the larger, ADAM, family generally "have the ability to degrade aggrecan" and suggests that Figure 4 of the specification shows a "metalloprotease domain alignment" placing the ADAMTS-E within the ADAMTS family, "imputing utility to the protein of the present invention" based on activities of

NO:2 herein shares a significant degree of sequence similarity with other members of the

family of mammalian ADAMTS metalloproteases, nothing in the record shows that all, or a majority, of the members of the ADAMTS family – or the larger ADAM family – share a common activity with a common substrate. The record instead shows that only a single ADAMTS metalloprotease functions as an aggrecanase, and the "31-59% identity in the metalloprotease domain [of the ADAMTS-E] . . . compared to other ADAMTS family member" that Applicant points to is insufficient to support any specific utility for the human ADAMTS-E having the amino acid sequence of SEQ ID NO:2 herein. The specification fails to demonstrate that the ADAMTS-E polypeptide recognizes and acts on any specific substrate, whether aggrecan, brevican, or some another component of extracellular substrates. Because the specification fails to identify a specific and substantial utility for the disclosed ADAMTS-E having the amino acid sequence of SEQ ID NO:2 herein described by claim 24, it cannot support a specific utility for the various, undisclosed, divergent genera of molecules described by claims 19-23 and 25-39, or the method of claim 14, at the time the application was filed.

In order to rely on the principles of the December 2000 Revised USPTO Utility Guidelines, Applicant must establish that claimed subject matter has a generally accepted utility. The record establishes no generally accepted utility, such as a common substrate recognized by all ADAM metalloproteases, or at least the ADAM-TS metalloprotease sub-family, that the ADAM-TS could share. The great divergence in identity of deduced metalloprotease amino acid sequences that Applicant alludes to at the close of page 8 of the Paper filed June 16, 2003, demonstrates that no correlation, rigorous or otherwise, between metalloprotease amino acid sequences can convey a specific utility from one member of the diverse families Applicant indicates to another. A method of use of a

confirming a "real world" context for its use, cannot be considered to be a substantial

utility". *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966). Mere allegations of a prospective, potential, utility cannot rise to the level of a credible assertion of a **specific** *in vivo* utility that is substantial and mere sequence similarity cannot support a **specific** *in vitro* utility that is substantial. The rejection of record is sustained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14 and 19-39 are also rejected, essentially for reasons of record, under 35 U.S.C. §112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to **use** the invention commensurate in scope with these claims.

Applicant's arguments filed June 16, 2003, have been fully considered but they are not persuasive. Applicant suggests at page 9 of the Paper filed June 16, 2003, that the claim amendments describing narrower genera of divergent metalloproteases in new claims 19-23 and 25-39 are adequate to overcome the rejection of record. Since the disclosed amino acid sequence of SEQ ID NO:2, described by claim 24 is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to **use** this claimed invention or the various, undisclosed, members of the divergent genera described by claims 19-23 and 25-30 or know how to usefully practice a method of claim 14, whether it depended from claim 19 or from claim 24. The rejection of record is sustained.

Claims 14, 19-23, and 25-39 are rejected, essentially for reasons of record, under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed

Applicant's arguments filed June 16, 2003, have been fully considered but they are not persuasive. Applicant suggests at page 9 of the Paper filed June 16, 2003, that the claim amendments describing narrower genera of divergent metalloproteases in new claims 19-23 and 25-39 are adequate to overcome the rejection of record. The rejection of record of divergent subject matter for lack of an adequate written description thereof is, however, maintained because specification fails to exemplify or describe the preparation of the subject matters of divergent ADAMTS-E polypeptides of claims 19-23 and 25-39 or a method of use the divergent ADAMTS-E polypeptides of claim 19 according to claim 14. New claims 19-23 and 25-39 reach genera of variant polypeptides having metalloprotease domains that differ from the 387-amino acid metalloprotease domain of SEQ ID NO:2 herein at as many as 38 amino acid positions in claim 19, at as many 4 positions in claim 22, and, while identical within this domain in claim 23, differing at any number of other amino acid positions elsewhere. New claims 25-39 reach genera of variant polypeptides having metalloprotease domains that differ, as in claim 19, at as many as 38 amino acid positions from the 387-amino acid metalloprotease domain of SEQ ID NO:2 herein with restrictions on the degree of variation in amino acid sequence positions of one other, further domain, yet differing at any number of other amino acid positions elsewhere.

Applicant's argument does not address the fact that the specification cannot describe **where** any difference in the amino acid sequence of SEQ ID NO:2 might occur, or **what** the difference might be. The specification does not otherwise disclose or suggest the nature or source of any of the generic proteins that meet the claim limitations. "While one does not need to have carried out one's invention before filing a patent application, one does need to be able to describe that invention with particularity" to satisfy the description

USPQ2d 1601 605 Fed. Cl. 1993 the specification furnishes no relevant

identifying characteristics of such variant polypeptides and the Court of Appeals for the Federal Circuit held that a claimed invention must be described with such "relevant identifying characteristic[s]" that the public could know that the inventor possessed the invention at the time an application for patent was filed, rather than by a mere "result that one might achieve if one had made that invention". *University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Indeed, like the claims invalidated by the appellate panel in *University of California v. Eli Lilly*, claims 14, 19-23, and 25-39 rejected herein are designed to embrace other, as yet unknown, human and mammalian polypeptides. Nothing demonstrates that, at the time the specification was filed, Applicant was "able to envision" enough of the structure of any of these undisclosed generic proteins to provide the public with identifying "characteristics [that] sufficiently distinguish it . . . from other materials". *Fiers*, 25 USPQ2d at 1604 (citing *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). The rejection of record is therefore sustained.

Claims 14, 19-23, and 25-39 are rejected, essentially for reasons of record, under 35 U.S.C. §112, first paragraph, because the specification is not enabling for embodiments of a metalloprotease having an amino acid sequence wherein a metalloprotease domain diverges that present in the amino acid sequence of SEQ ID NO:2 by amino acid substitutions, deletions and insertions, or combinations thereof at as many as 38 amino acid positions, or even 4 amino acid positions, within SEQ ID NO:2 and that differs by any number of amino acid positions elsewhere. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Applicant's arguments filed June 16, 2003, have been fully considered but they are not persuasive. Applicant suggests at page 9 of the Paper filed June 16, 2003, that the claim amendments describing narrower genera of divergent metalloproteases in new claims 19-23 and 25-39 are adequate to overcome the rejection of record. The rejection of

'9 contemplate arbitrary assignments of any or all of amino acid substitutions, additions

deletions in multiple genera of metalloproteases having as many as 38 amino acid sequence variations in metalloprotease domains relative to that present in SEQ ID NO:2, in the case of claims 14, 19, and 25-39, or as few as amino acid sequence variations in that domain in claims 20-22, and differing at any number of positions outside the metalloprotease domain in the case of claim 23. No claim describes a fusion protein that comprises the integral, identical, metalloprotease set forth in the 1104-amino acid sequence of SEQ ID NO:2. The specification cannot support introduction of even a few amino acid insertions, deletions, or substitutions in the amino acid sequence of SEQ ID NO:2, because it does not teach where these alterations may occur anywhere, in any combination or any pattern, in the amino acid sequence set forth in SEQ ID NO:2. Indeed, neither the prior art made of record herewith nor in Applicant's Information Disclosure of Paper No. 6 can identify, taken together with the specification, a few amino acids in the primary sequences of members of the family of human ADAMTS metalloproteases that might be altered, nor teach the nature of an alteration that may be made, which permits a resulting polypeptide to support its native function. Mere sequence perturbation cannot enable the design and preparation of divergent metalloproteases that will provide the public with an enzyme that retains its native function, a function not taught by the specification.

It is well settled that 35 U.S.C. §112, first paragraph, requires that a disclosure be sufficiently enabling to allow one of skill in the art to practice the invention as claimed without undue experimentation and that unpredictability in an attempt to practice a claimed invention is a significant factor supporting a rejection under 35 U.S.C. §112, first paragraph, for non-enablement. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (recognizing and applying the "*Forman*" factors). Cf., *Ex parte Forman*, 230 USPQ

-nablement - the standard set by the CCPA, the predecessor of the Court of Appeals for

the Federal Circuit, is not to "make and screen" any and all possible alterations because a reasonable correlation must exist between the scope asserted in the claimed subject matter and the scope of guidance the specification provides. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 25 (CCPA 1970). The Federal Circuit approved the standard set by the CCPA in *Genentech, Inc. v. Novo-Nordisk A/S*, 42 USPQ2d 1001 (Fed. Cir. 1997). The scope of subject matters embraced by claims 14, 19-23 and 25-39 is unsupported by the present specification even if taken in combination with teachings available in the prior art, therefore the rejection of record is sustained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 14, 19-23, and 30-34 are for reasons of record rejected under 35 U.S.C. §102(e) as being anticipated by Heller et al., published U.S. Patent Application No. 2002/0107361, of record.

Applicant's arguments filed June 16, 2003, have been fully considered but they are not persuasive. The claims rejected herein are based on the disclosure of Applicant's U.S. Provisional application filed April 26, 2000, thus Applicant's argument that the disclosure of Heller et al. having the priority date of a U.S. Provisional application filed February 18, 2000 – two months before Applicant's earliest priority date – is not cognizable. Heller et al. disclose the amino acid sequence of the MPTS-10 human metalloprotease, see SEQ ID

position 134 in the amino acid sequences of SEQ ID NO:3 of Heller et al. and of SEQ ID NO:2 herein, and the MPTS-10 amino acid sequence further comprises a prodomain completely identical in sequence to the prodomain sequence of SEQ ID NO:2 herein. Thus Heller et al. clearly meet the limitations of claims 19-23 and 30-34 herein. The disclosure of Heller et al. at paragraphs 0080-0087 also meets the limitations of claim 14 herein, wherein an MPTS metalloprotease is used in assays to identify compounds capable of inhibiting MPTS metalloprotease activity in which a purified composition of a MPTS metalloprotease is contacted with a candidate inhibitory compound and the extent of inhibition determined. The rejection of record is therefore maintained.

Conclusion

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 703.308.0583. The examiner can normally be reached between 9:00AM-5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached at 703.308.3804. Further fax phone numbers for the organization where this application or proceeding is assigned are 703.308.4242 for regular communications and 703.308.0294 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703.308.0196.

William W. Moore
September 5, 2003